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SNP PROFILING OF KIDNEY TRANSPLANT PATIENTS: HIGHLIGHTING THE DIFFERENCES IN THE GENETICAL BACKGROUND TO MAXIMIZE IMMUNOSUPPRESSIVE THERAPIES

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Introduction: Acute renal allograft rejection is defined as a sudden decline in the function of the transplanted kidney that gives rise to the creatinine levels. Whenever acute rejection is confirmed, the possibility of inadequate immunosuppression, whether due to inadequate dosing or noncompliance, must be addressed. The failure to recognize this contributing factor increases the risk of continued acute rejection episodes and, due to inadequate long-term immunosuppression, may eventually lead to graft failure. However, there is not a pre-defined protocol available to predict the probability of an adverse event in patients receiving the same medications. Moreover a more personalized immunosuppressive therapy may prevent complications and help to avoid graft rejection. Several Single Nucleotide Polymorphisms (SNPs) have been already associated with acute renal allograft rejection (AR). Therefore we aim to identify a pre-operative SNP profile assay that might underline the differences in the genetic background of the patients. SNPs are analyzed for allele and genotype frequencies in genes involved in immune responses and pharmacokinetics/pharmacodynamics of immunosuppressive drugs.

Methods: This is a cohort study. Genomic DNA isolated from 200 µl of whole blood of 153 kidney transplant patients (42 with AR (wAR) and 111 without AR (w/oAR)) are genotyped for 20 SNPs in TNF-alpha, IL-10, ABCB1, UGT1A9, IMPDH2 genes.

Results: The average age of our kidney transplanted patients is 52.8 years and their group consists of 48 females and 105 males. Based on our preliminary results all SNPs are in Hardy-Weinberg equilibrium (HWE) in our study population. No transplant patients wAR were C/C homozygote for ABCB1 G-2677T/A, T/T and C/C homozygotes for UGT1A9 C-440T and T-331C, respectively. In our ongoing study so far 9 SNPs have been analyzed by Trend Test between the two transplanted groups; the p values are above 0.05 for each SNP, with the exception for UGT1A9 C-440T and T-331C (p = 0.043). The allele frequencies of C for UGT1A9 C-440T and T for UGT1A9 T-331C are both 70% in the w/oAR group; while, the allele frequencies of those polymorphisms are increased to 83% in the wAR group.

Conclusions: The homozygotes T/T and C/C for UGT1A9 C-440T and T-331C are missing in the wAR group and may define a possible protective haplotype for patients w/oAR. However, analyzing the composition of the two transplant groups there is a statistically significant difference for gender. Thus, to confirm our results a case-control, multicenter research study is needed. Data from the newly enrolled patients will allow us to perform an age- and sex-matched analysis of the patients' cohort. Understanding the exact link between these SNPs and acute kidney rejection is crucial to more successfully maximize antirejection therapies.

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SHARED AND ENDORGAN SPECIFIC TRANSCRIPTIONAL NETWORKS IN SKIN VERSUS KIDNEY BIOPSIES IN SYSTEMIC LUPUS

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Introduction: Skin rash can often herald the onset of a systemic disease flare in systemic lupus. Further, the subtype of skin lesion may confer a differential risk of renal involvement. We hypothesized that renal flares may be triggered via a crosstalk between skin and kidneys and that similar molecular mechanisms may underlie skin and renal disease. We used systems biology approaches to integrate the regulatory events occurring specifically in subacute cutaneous lupus erythematosus (sCLE) and discoid lupus erythematosus (DLE) and compared with those in LN.

Methods: Formalin-fixed paraffin-embedded tissue from 7 normal, 26 DLE and 23 sCLE rash biopsies were analyzed via microarrays. Gene expression profiles from 22 LN (9 WHO III and 13 WHO IV) and 14 healthy microdissected human renal biopsies (ERCB) were compared. Genomatix and Ingenuity softwares were used for downstream analyses.

Results: Analysis of SLE skin lesions. The comparison across DLE and sCLE vs normal skin identified a shared network of genes known to be differentially regulated in systemic lupus (e.g. IFNγ, IL2, IL4, IL6, TLR4). Distinct transcriptional programs were seen with the regulation of PPAR, B-cell receptor, HIF1α and IL6 signaling highlighted unique to DLE, whereas metabolic and immune responses predominated in sCLE, with unique ITGB2, ITGB8, MMP1, TIMP1 expression. Transcriptomic comparison of SLE skin lesions and lupus nephritis kidneys. Shared transcriptional networks in SLE skin lesions versus LN kidney biopsies reflect similar pathway activation. Respectively 986 and 783 genes were regulated in the same direction in the glomeruli of LN patients vs controls and in DLE and sCLE vs normal (q-value <0.05). The 282 genes regulated only in the LN glomeruli and DLE rashes represented a mainly down-regulated network highlighting MAPK3, MEP1B, LCK, PPARGC1A, CCL2 and PTEN as main nodes. Top pathways included PTEN and chemokine signaling. The 82 genes specific to LN glomeruli and sCLE showed a mainly up-regulated network with CD40 as major node. Ingenuity top pathway was FLT3 signaling in hematopoietic progenitor cells. FLT3LG is essential in the development and related processes of dendritic cells, which may play a role in cutaneous and renal lupus pathogenesis.

Conclusions: DLE and sCLE have overlapping and unique transcriptional expression signatures. Further analysis of these specific profiles suggests that DLE, which is less associated with renal involvement, demonstrates repression of inflammatory pathways which could predict protection from renal disease. Contrarily, sCLE, which is associated with a higher risk of lupus nephritis, shares overlapping gene regulation involving dendritic cells which may identify this cellular population as essential to disease development for both skin and renal disease. These data may identify important molecular targets for novel therapies in cutaneous and renal lupus.